OPEN ACCESS

Impact of adalimumab in patients with active non-infectious intermediate, posterior, and panuveitis in real-life clinical practice: HOPE study

Uwe Pleyer ,[1] Salem Al-Mutairi,[2] Conor C Murphy ,[3] Rola Hamam,[4] Shereen Hammad,[5] Orsolya Nagy,[6] Zsuzsanna Szepessy,[7] Yan Guex-Crosier ,[8] Karina Julian,[9,10] Zohar Habot-Wilner,[11] Sofia Androudi [12]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjo-2021-320770).

For numbered affiliations see end of article.

Correspondence to
Dr Uwe Pleyer, Charité Universitätsmedizin Berlin, Berlin, Berlin, Germany; uwe.pleyer@charite.de

KJ, ZH-W and SA contributed equally.

Results of this study were presented, in part, at the ACR Convergence 2020: the American College of Rheumatology's All-Virtual Annual Meeting, 5–9 November 2020.

Received 15 November 2021
Accepted 22 September 2022
Published Online First 19 October 2022

ABSTRACT

Background/Aim This study evaluated real-life adalimumab impact in patients with active non-infectious intermediate, posterior, or panuveitis (NIIPPU).

Methods Adults with active NIIPPU received adalimumab in this prospective, observational study (06/2017–04/2020). Patients were evaluated at baseline (V0) and four follow-up visits over 12 months (V1–V4). Primary endpoint: proportion of patients achieving quiescence (anterior chamber (AC) cells grade and vitreous haze (VH) grade≤0.5+ in both eyes, no new active chorioretinal lesions) at any follow-up visit. Secondary endpoints: proportion of patients achieving quiescence at each visit; proportion of patients maintaining response; and proportion of patients with flares. Workability, visual function, healthcare resource utilisation, and safety were evaluated.

Results Full analysis set included 149 patients. Quiescence at any follow-up visit was achieved by 129/141 (91%) patients. Quiescence at individual visits was achieved by 99/145 (68%), 110/142 (77%), 102/131 (78%), and 99/128 (77%) patients at V1–V4, respectively. Number of patients in corticosteroid-free quiescence increased from 51/147 (35%; V1) to 67/128 (52%; V4; p<0.05). Proportion of patients with maintained response increased from 89/141 (63%; V2) to 92/121 (76%; V4; p<0.05) and proportion of patients with flare decreased from 25/145 (17%; V1) to 13/128 (10%; V4; p=0.092). Workability and visual function improved throughout the study. Proportion of patients with medical visits for uveitis decreased from 132/149 (89%; V0) to 27/127 (21%; V4). No new safety signals were observed.

Conclusion These results demonstrated adalimumab effectiveness in improving quality of life while reducing economic burden of active NIIPPU.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Clinical studies found that adalimumab is effective and safe in patients with non-infectious intermediate, posterior, and panuveitis (NIIPPU).

WHAT THIS STUDY ADDS

⇒ This is the first study to date to demonstrate real-life effectiveness of adalimumab in patients with active NIIPPU. Adalimumab improved inflammation, quality of life, and workability, as well as reduced the economic burden of NIIPPU.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This real-world study assessed effectiveness of adalimumab in a large international cohort of patients; the results of this study suggest that adalimumab can be safely and effectively used in a clinical practice.

INTRODUCTION

Non-infectious uveitis is an immune-mediated intraocular inflammatory disease that can lead to vision impairment and blindness.[1 2] Uveitis can have a substantial economic burden as a result of visual impairment and associated loss of productivity.[2] Non-infectious intermediate, posterior, and panuveitis (NIIPPU) was associated with greater annual direct healthcare resource utilisation (HRU), higher healthcare costs, and greater risk of workability loss compared with a matched population without uveitis.[3] Corticosteroids are typically the first-line of therapy for controlling ocular inflammation; however, prolonged corticosteroid use can lead to ocular and systemic adverse events (AEs).[4 5] After achieving treatment response, the recommendation is to taper and, if possible, discontinue corticosteroids.[5] In clinical practice, therapeutic options for NIIPPU management now include corticosteroid-sparing immunosuppressants such as non-biologic disease-modifying antirheumatic drugs (DMARDs; eg, azathioprine, methotrexate) that can be used to supplement corticosteroid therapy.[6 7]

Adalimumab (Humira, AbbVie, North Chicago, Illinois, USA), a monoclonal antibody that targets tumour necrosis factor-α (TNFα) as a biologic DMARD, has been approved for the treatment of NIIPPU.[8] Efficacy and safety of adalimumab in patients with active or inactive NIIPPU was demonstrated in the VISUAL I and II clinical trials and the VISUAL III open-label extension study.[9–12] The VISUAL III study suggested that adalimumab can provide long-term control of NIIPPU.[11 12]

The goals of uveitis therapy are to suppress inflammation and achieve quiescence, prevent flares, and maintain good visual function.[13] There are limited data available on the effects of adalimumab on NIIPPU in routine clinical settings using

Check for updates

To cite: Pleyer U, Al-Mutairi S, Murphy CC, *et al*. *Br J Ophthalmol* 2023;**107**:1892–1899.

quiescence as a primary endpoint. Additionally, better understanding of real-world disease characteristics, aetiologic origin, and underlying systemic diseases are needed.

This study evaluated real-life effectiveness of adalimumab in patients with active NIIPPU despite corticosteroid therapy. Disease characteristics and effects of adalimumab on treatment response (quiescence), health-related quality of life, workability, and HRU in real-world settings were assessed.

METHODS

Study design and patients

HOPE (impact of adalimumab *th*erapy on *o*cular inflammation, selected HRU and *p*atient *re*ported outcomes in patients with active NIIPPU in routine clinical practice; NCT03155243) was a 12-month, postmarketing, prospective, observational study at 24 sites in 12 countries (online supplemental table 1). Patient enrolment was from 20 June 2017 to 24 February 2020, with database lock on 20 April 2020. Included in the study were patients aged ≥18 years with active NIIPPU. Uveitis was classified according to the Standardization of Uveitis Nomenclature (SUN).[14] The decision to treat with adalimumab was made before any decision to approach a patient to participate in this study. Excluded were patients who could not be treated with adalimumab per local prescription guidelines, had prior adalimumab treatment, participated in other clinical studies, or were unwilling or unable to complete patient-reported questionnaires. Patient visits included baseline (V0) and follow-up visits over 12 months at 3-month intervals (V1, V2, V3, and V4). Patient sociodemographic data and NIIPPU-specific medical history were collected at V0. In accordance with the approved adalimumab label,[8] screening for active or latent tuberculosis (TB) was recommended for all patients.[8] Screening for demyelinating disease (medical history and/or neurological examination) was recommended for all patients with intermediate uveitis before initiating adalimumab treatment.[8]

Efficacy assessments

The primary endpoint of this study was the proportion of patients achieving quiescence (AC cells grade≤0.5+ on slit lamp examination according to the SUN Working Group criteria[14] and VH grade≤0.5+ as described in the National Eye Institute Criteria adapted by the SUN Working Group[14 15] in both eyes and no new active chorioretinal inflammatory lesions) at any of the follow-up visits.

Secondary endpoints included the proportion of patients achieving quiescence at each visit separately; the proportion of patients who maintained response (quiescence achieved at prior visit and no flare at current visit) at any follow-up visit and at each visit separately; the proportion of patients with sustained maintained response (defined as quiescence achieved at all respective prior visits and no flare at current visit) at each visit separately; and the proportion of patients with flares (AC cells grade≥2+, or VH grade≥2+ in ≥1 eye and new active inflammatory lesions) at any follow-up visit. Proportions of patients with corticosteroid-free quiescence (ie, not receiving any type of systemic or local corticosteroids when quiescence was observed) were assessed at all visits. Evaluations were assessed for both eyes at all follow-up visits and included change in central retinal thickness (CRT) measured by optical coherence tomography, best corrected visual acuity (BCVA), and intraocular pressure.

Patient-reported outcomes were assessed at V0, V2 (6 months). and V4 (12 months). Effects on workability were evaluated using Work Productivity and Activity Impairment–Uveitis (WPAI-UV) scores. Absenteeism, presenteeism, and daily activity impairment were assessed with the WPAI-UV questionnaire.[16] Visual function was assessed with the National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25)[17] using 12 subscale scores and composite scores.

HRU assessment at V0 included visits for uveitis in the preceding 6 months. These data were evaluated at V2–V4 by medical visits for uveitis since the last visit. Visits to a healthcare professional, emergency room visits and hospital admissions were included in the analysis. Cumulative healthcare visits summarised the number of visits to healthcare professionals, number of emergency room visits, and the number of hospital admissions.

Changes in concomitant medication and immunosuppressant load were assessed at each visit. Serious AEs (SAEs), AEs of special interest (AESI), pregnancies, and product complaints were collected.

Analysis methods

The full analysis set (FAS) included all patients enrolled who fulfilled the patient selection criteria and had data for ≥1 follow-up visit. Data were analysed descriptively. Two-sided 95% CIs were calculated where appropriate. For quiescence and flare variables, as observed in the analysis in FAS patients, valid data was used without imputation. For patient-reported outcomes, last observation carried forward (LOCF) analysis was carried out for missing values at V4. P values were calculated using t-test or χ^2 test.

RESULTS

Patient disposition and baseline characteristics

Of 155 patients enrolled, 149 patients were included in the FAS and 106 completed the study with no adalimumab discontinuations. FAS patients were assessed at V0 (n=149), V1 (n=147), V2 (n=143), V3 (n=134), and V4 (n=128). During the follow-up period, 21/149 (14%) of FAS patients discontinued the study. Reasons for discontinuation were AEs (n=5), SAEs or AESI (n=3), lost to follow-up (n=8), investigator decision (n=10), and patients request (n=8; online supplemental figure 1); some patients had multiple reasons for discontinuation. Mean age at baseline was 42.3 years; 93/149 (62%) of patients were women, and 120/149 (81%) were white (table 1). Most patients were working (89/149; 60%), and 74 of those were working full-time; 26/149 (17%) of patients were unemployed but seeking work or a homemaker, 13/149 (9%) were on sick leave, and 11/149 (7%) were unemployed due to disability (table 1). Of 13 patients on sick leave, 8 were on leave because of NIIPPU. Most patients had been diagnosed with NIIPPU for >3 years before study inclusion. After first onset of symptoms, it was an average of 4.5 months until NIIPPU diagnosis and an additional 2.5 months until initiation with any NIIPPU-indicated treatment.

The NIIPPU aetiology was idiopathic in 75/149 (50%) of patients. In 119/149 patients, both eyes were affected (80%). Panuveitis was the most common anatomical NIIPPU type (64/149; 43%). Patients experienced an average of 2.2 flares in the 12 months before study inclusion. The majority of patients experienced prior ocular complications (96/149; 64%); most common was macular oedema; (62/149; 42%; table 1). Furthermore, 119/149 (80%) patients reported ocular complications at the time of study inclusion; most common was macular oedema (80/149; 54%; table 1).

Mean±SD time from V0 to first adalimumab administration was 8±26 days and mean duration of adalimumab treatment

Table 1 Baseline demographics and patient characteristics

Variable	Full analysis set (N=149)
Age, mean±SD, y	42.3±15.2
Female sex, n (%)	93 (62)
Race, n (%)	
White	120 (81)
Asian	2 (1)
Black	1 (0.7)
Other	26 (17)
Employment status,* n (%)	
Working for payment	89 (60)
Unemployed but seeking work or homemaker	26 (17)
Unemployed due to disability	11 (7)
Retired	16 (11)
Sick leave	13 (9)
Student	11 (7)
Mean±SD number of flares in the past 12 months	2.2±1.8
Systemic NIIPPU-indicated therapy,* n (%)	
Any	78 (52)
Prednisone/methylprednisone	64 (43)
Methotrexate	17 (11)
Azathioprine	12 (8)
Highest daily prednisone or equivalent dose, mg	
Median (25% quartile, 75% quartile)	48.0 (16, 60)
Anatomic localisation of uveitis,*† n (%)	
Panuveitis	64 (43)
Intermediate	45 (30)
Posterior	45 (30)
Aetiologic origin,* n (%)	
Any	149 (100)
Idiopathic	75 (50)
Behçet syndrome	25 (17)
Vogt-Koyanagi-Harada	13 (9)
Sarcoid	11 (7)
Birdshot chorioretinopathy	6 (4)
Other	23 (15)
Past ocular complications, n (%)	
Any‡	96 (64)
Macular oedema	62 (42)
Cataract	46 (31)
Vision loss	36 (24)
Glaucoma	29 (19)
Retinal detachment	6 (4)
Other	26 (17)
Ocular complications at time of study inclusion, n (%)	
Any‡	119 (80)
Macular oedema	80 (54)
Vision loss	40 (27)
Cataract	38 (26)
Glaucoma	27 (18)
Retinal detachment	6 (4)
Other	35 (24)
Mean central retinal thickness±SD, µm	
Left eye (n=135)	306.9±107.7
Right eye (n=131)	306.9±124.9
Mean BCVA±SD, logMAR	
Left eye (n=146)	0.7±0.5
Right eye (n=142)	**0.7**±0.4

*Multiple entries were possible.
†According to Standardisation of Uveitis Nomenclature criteria.
‡Patients with any complications.
BCVA, best corrected visual acuity; NIIPPU, non-infectious, intermediate, posterior, or panuveitis.

was 216±93 days. Of patients screened for TB, 8/144 (6%) were quantiferon positive; 7 of those completed TB prophylaxis≥4 weeks before adalimumab initiation.

Effectiveness

The primary endpoint, quiescence, was achieved by 129/141 patients (91%) with assessment data at any of the follow-up visits (figure 1A). Most patients achieved quiescence at each visit; the proportion of patients who achieved quiescence was 99/145 (68%) at V1, 110/145 (77%) at V2, 102/131 (78%) at V3, and 99/128 (77%; figure 1B) at V4. Overall, the proportion of patients who achieved corticosteroid-free quiescence increased from 51/147 (35%) at V1 to 67/128 (52%) at V4; p<0.05. Of those who achieved quiescence, the proportion of FAS patients with available data who were corticosteroid-free changed from 51/99 at V1 (52%) to 67/99 (68%; figure 1C) at V4.

Response was maintained in 115/138 (83%) of patients at any of the follow-up visits (figure 2A); the proportion of patients with maintained response increased from 89/141 (63%) at V2 to 92/121 (76%; figure 2B) at V4; p<0.05. Sustained maintained response (quiescence achieved at all respective prior visits and no flare at the current visit) was reported in 89/141 (63%) at V2, 77/129 (60%) at V3, and 68/121 (56%) at V4. Flares occurred in 41/127 (32%) patients at any of the follow-up visits (figure 2C); the proportion of patients who had a flare decreased from 25/145 (17%) at V1 to 13/128 (10%) at V4 (p=0.092; figure 2D).

Mean±SD CRT decreased from 307±125 µm at V0 to 289±109 µm at V4 in the right eye (mean change, 11±145 µm; p=0.47) and 307±108 µm at V0 to 281±64 µm at V4 in the left eye (mean change, 33±88 µm; p=0.0007). BCVA remained stable (mean worsening of 0.7 logMAR at V0 to 0.8 logMAR at V4).

Patient-reported outcomes and HRU

Patient-reported visual function improved at V4 compared with V0 (online supplemental figure 2). For VFQ-25, the median overall composite score increased from 72.5 points (IQR, 55.8–89.1) at V0 to 88.2 points (IQR, 66.6–95.1) at V4. Median change in overall VFQ-25 score vs baseline was 3.3 (IQR, 0.4–13.4) at V2 and 4.7 (IQR, 0.4–14.4) at V4-LOCF (p<0.0001).

Workability parameters improved in all categories at V4 vs V0, including total activity impairment, total work productivity impairment, absenteeism, and presenteeism (figure 3A). The median change in total activity impairment compared with baseline was 0 (IQR, −30.0 to 0.0) at V2 and −10 (IQR, −40.0 to 0) at V4. The proportion of patients with medical visits for uveitis in the preceding 6 months or since the last visit decreased from V0 to V4 (figure 3B). During the 6-month period before V0, the proportion of patients with medical visits for uveitis was

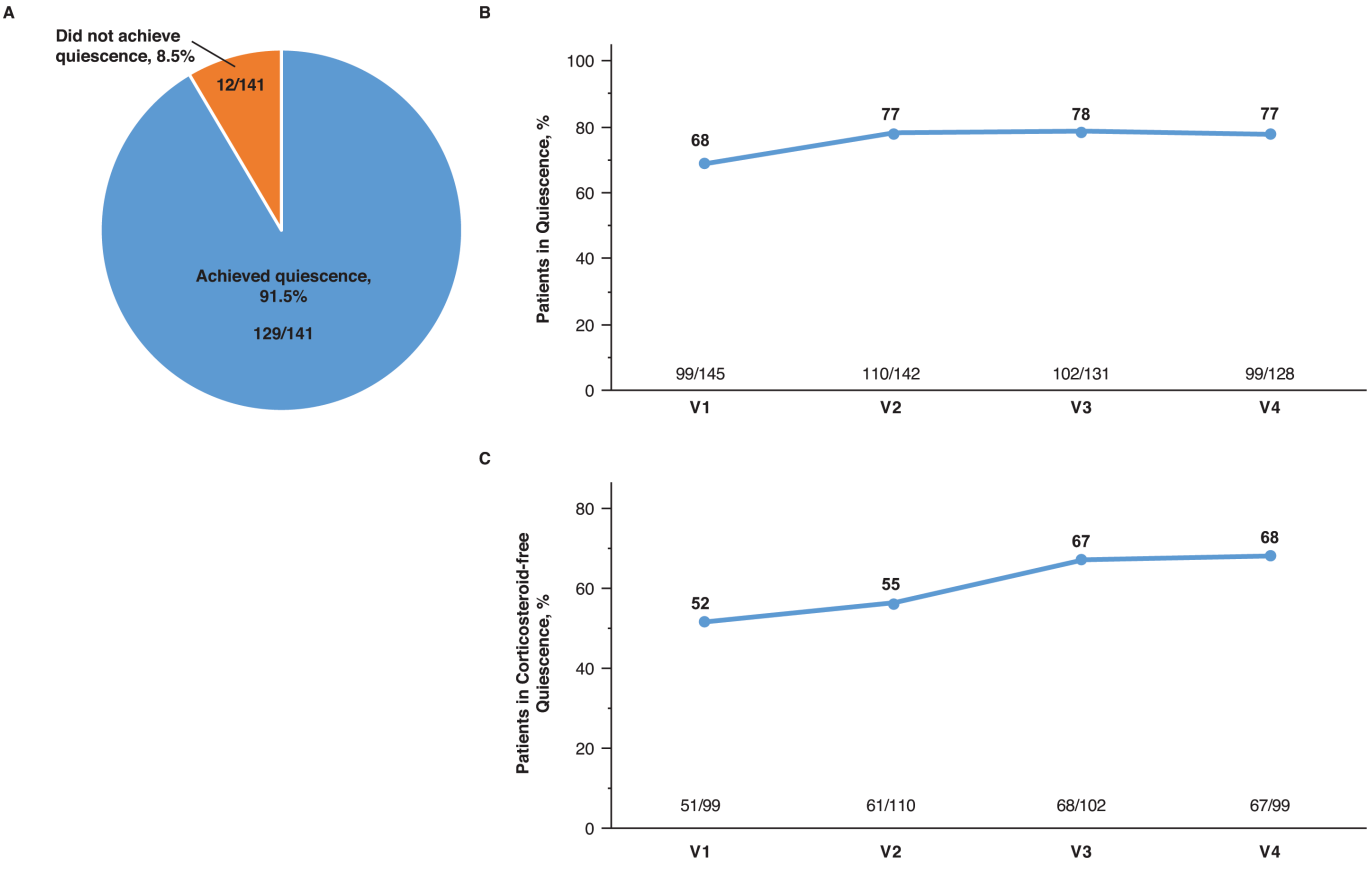


Figure 1 Proportion of patients who achieved quiescence* at any visit during follow-up (A) and at separate follow-up visits (B). Proportion of patients in quiescence who were corticosteroid-free at separate follow-up visits (C). Visit schedule included baseline visit (V0) and four follow-up visits over 12 months at 3-month intervals (V1, V2, V3, and V4). *No new active chorioretinal inflammatory lesions and AC cells ≤0.5+ and VH grade≤0.5+ in both eyes. AC, anterior chamber; VH, vitreous haze.

132/149 (89%). At V4, 27/127 patients (21%) had any visits for uveitis since the last study visit. Emergency room visits for uveitis decreased from 35/132 (27%) before V0 to 0% at V4. Furthermore, hospital admission among patients with a visit for uveitis was 14/132 (11%) before V0; none were admitted to the hospital during V1–V4 follow-up period (figure 3B).

Concomitant therapy

The most common concomitant systemic therapies were prednisone, methotrexate, and azathioprine. The proportion of patients receiving ≤7.5 mg/day prednisone equivalent was 95/149 (64%) at V0 and 99/128 (77%) at V4. Some patients with Vogt-Koyanagi-Harada, sarcoid, Behçet syndrome, or serpiginous chorioretinopathy required high supplementary corticosteroid doses.

Three outliers received disproportionately high corticosteroid doses. Two patients received 1250 mg/day prednisone equivalent as highest maintenance dose: one patient received it as a pulse therapy at V1, and one patient received it for an unknown duration. One of these patients had Behçet syndrome, cataract, and macular oedema, and the other had Vogt-Koyanagi-Harada and vision loss at V0. One other patient with Vogt-Koyanagi-Harada and macular oedema received 312.5 mg/day prednisone equivalent as highest maintenance dose. When these three patients were excluded from analysis, mean prednisone equivalent dose decreased from 18.5 mg/day at V0 to 10.6 mg/day at V4 (p=0.004).

The proportion of patients receiving local corticosteroids, administered as injections, intravitreal implants (dexamethasone implants were used in four patients), or topical eye drops, changed from 47/149 (32%) at V0 to 31/128 (24%) at V4. The most common NIIPPU-indicated local corticosteroids were prednisone and dexamethasone.

Safety

In FAS patients, 13/149 had SAEs (9%; table 2). When analysed by system organ class, most common AEs were infections (4/149; 3%) and eye disorders (3/149; 2%). All pregnant patients (3/149; 2%) discontinued adalimumab per investigator decision despite being permissible per adalimumab label.[8] The majority of reportable events were non–life-threatening and were not considered to have a causal relationship to adalimumab. When analysed by frequency distribution based on individual events, most reportable events were resolved or resolving (21/27; 78%) and were mild-to-moderate in severity (23/27; 85%).

DISCUSSION

This study assessed adalimumab impact in real-life clinical practice and provided comprehensive and detailed characteristics of an international patient population with NIIPPU receiving adalimumab. To date, this is the only real-world prospective study to address adalimumab impact on quality of life, workability, and HRU. The patient population was diverse and with complex aetiology, including a substantial number of patients with Behçet

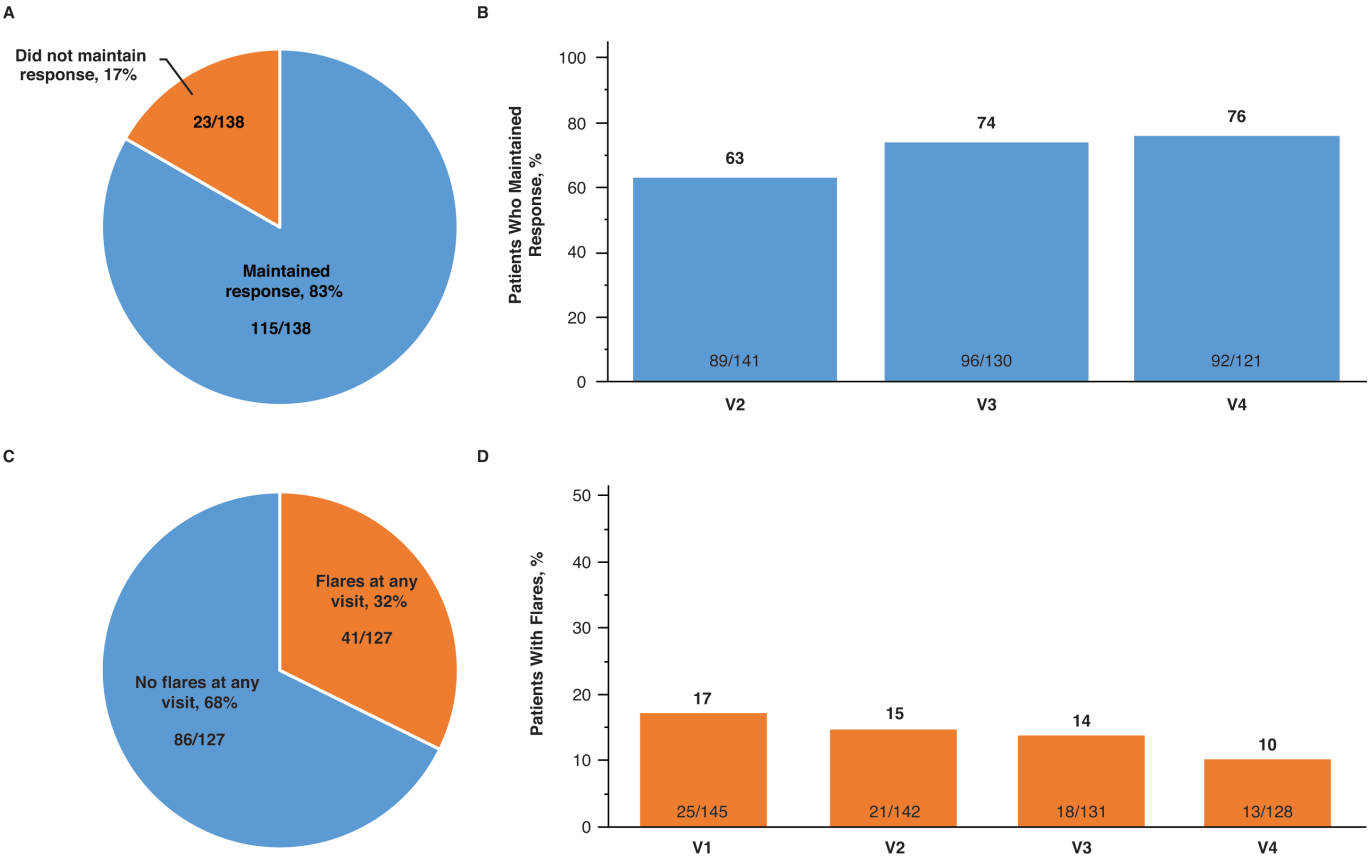


Figure 2 Proportion of patients who maintained response* at any visit during the follow-up (A) and at separate follow-up visits (B) and proportion of patients who had flare† at any visit (C) and at separate follow-up visits (D). *Quiescence achieved at prior visit and no flare at current visit. †New active inflammatory lesions, AC cell grade≥2+, or VH grade≥2+ in ≥1 eye. AC, anterior chamber; VH, vitreous haze.

disease, Vogt-Koyanagi-Harada's, and birdshot chorioretinopathy, which may have increased the challenge of treatment. The mean time between the first onset of symptoms and treatment initiation was 7 months (4.5 months between the onset of symptoms and diagnosis and 2.5 months between diagnosis and treatment), indicating potentially limited access to uveitis specialists. Discontinuation rate in this study (21/149; 14% of FAS patients) is consistent with the discontinuation rates in the VISUAL I study, where 18/110 (16%) patients receiving adalimumab discontinued the study during the follow-up period of 52 weeks.[9]

Uveitis-specific endpoints used to assess treatment efficacy can vary among studies. The VISUAL I and II studies reported that adalimumab therapy was associated with lower risk of uveitis recurrence or visual acuity loss compared with placebo during and after the mandatory corticosteroid taper following the initial corticosteroid burst.[9 10] In patients with active uveitis at study entry, the VISUAL III open-label study assessing long-term adalimumab effects reported an increase in proportion of patients in quiescence from 8% (19/240) at baseline to 80% (98/123) at week 150.[12] A small real-world prospective cohort study in patients with non-infectious uveitis (n=43) reported that 91% of patients receiving TNFα inhibitors achieved sustained remission (anterior chamber inflammation and vitreous haze scores of ≤0.5+ on two successive visits, absence of retinal vasculitis, or worsening cystoid macular oedema).[18] Another real-world retrospective study (n=106) reported that 84% of patients receiving adalimumab achieved ocular control (absence of ocular flare in both eyes and reduction of prednisone-equivalent dose to ≤10 mg/day or halving the initial steroid dose; ocular flare: AC cells grade or VH grade≥1+, or active chorioretinal lesions, inflammatory retinal vascular lesions, or optic nerve inflammation) within 6 months.[19]

Although differences in study design and methodology make it difficult to compare outcomes, the association of TNFα inhibitors with remission of ocular inflammation in patients with non-infectious uveitis is consistent with the results of the current study. The current study did not have a mandatory corticosteroid burst or taper. Quiescence was achieved by 129/141 (92%) of patients at any of the four visits during the 12-month follow-up; most patients (68%–78%) achieved quiescence at individual follow-up visits through month 12 based on 'as observed' analysis, a less conservative approach to report quiescence results. Using a post hoc intention-to-treat (ITT) analysis, the quiescence rates were 99/149 (66%), 110/149 (74%), 102/149 (68%), and 99/149 (66%) at V1, V2, V3, and V4, respectively, demonstrating a stable response across all visits. Response was maintained in 115/138 (83%) of patients at any of the follow-up visits, and sustained response was maintained by 68/121 (56%) of patients at V4. Of note, quiescence rates in the VISUAL I study ITT analysis study decreased from~50% at week 12 to~20% at week 52[20]; however, in the steroid tapering was mandatory by week 15 in the VISUAL I randomised clinical trial.

Based on a claims analysis in the USA, patients with NIIPPU had 2.9 times higher medical costs and 4.7 times higher prescription drug costs compared with matched controls, underscoring the economic burden of disease. Medically related absenteeism and work loss were significantly greater in patients with NIIPPU compared with matched controls (p<0.0001).[3]

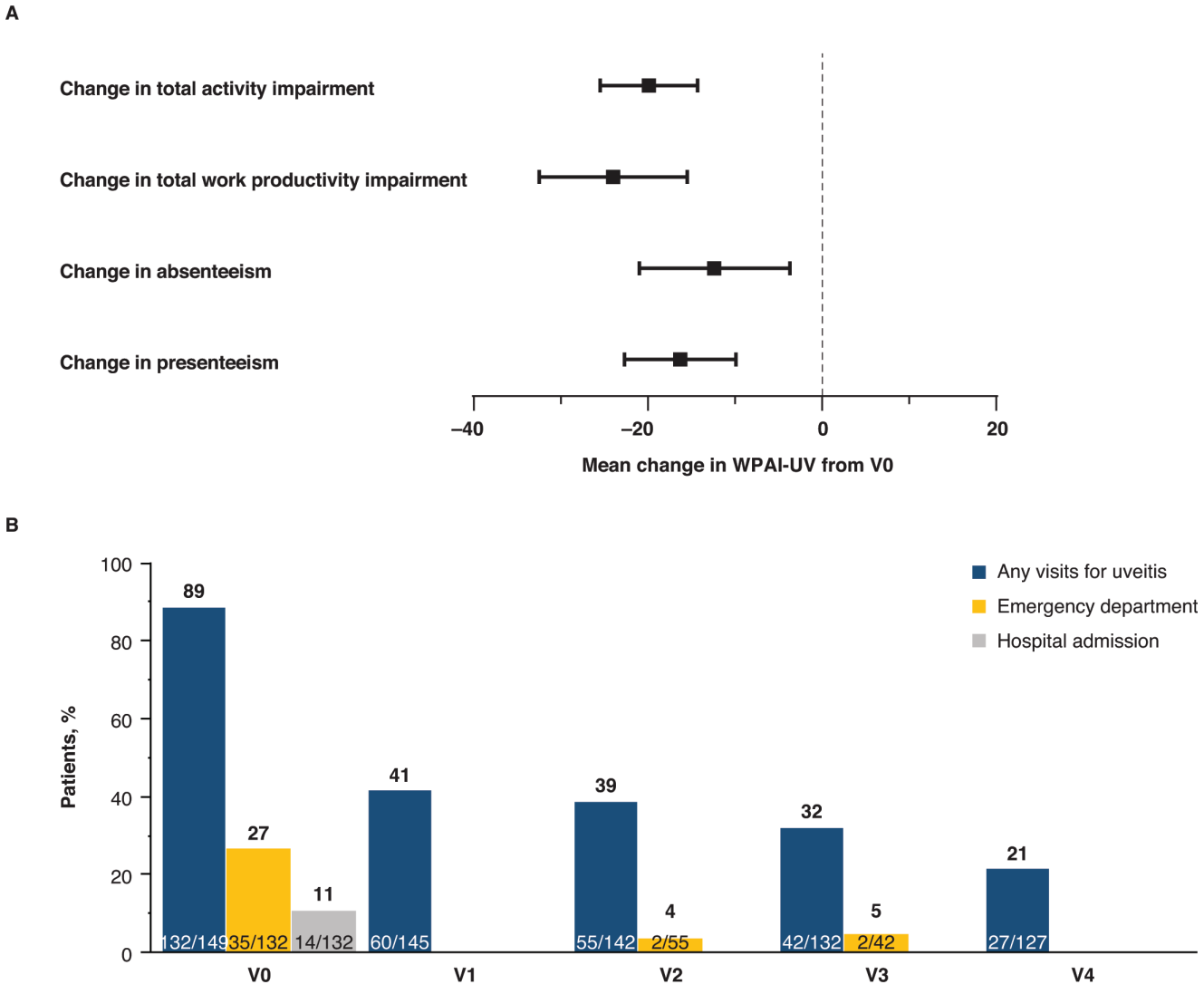


Figure 3 Mean change in WPAI-UV at V4 vs V0 (A); visits included baseline visit (V0) and follow-up visits at V2 and V4. Proportion of patients who had any medical visits for uveitis and, of those patients, proportion who reported emergency room visits and hospital admissions (B). Visit schedule included baseline visit (V0) and four follow-up visits over 12 months at 3-month intervals (V1, V2, V3, and V4). WPAI-UV, Work Productivity and Activity Impairment–Uveitis.

In this real-world analysis of patients with NIIPPU, adalimumab was associated with a decrease in HRU and improved patient-reported outcomes, including visual function and workability. At V4, only 27/127 (21%) of patients had a medical visit for uveitis since their last study visit, compared with 132/149 (89%) of patients who had a medical visit for uveitis during the 6 months before V0. There was a decrease in emergency room visits for uveitis (0/27 at V4 vs 35/132 (27%) before V0) and hospital admission among patients with a visit for uveitis (0/27 at V4 vs 14/132 (11%) before V0). Adalimumab was associated with improvements in overall VFQ-25 scores and WPAI-UV scores for total activity impairment, work productivity impairment, absenteeism, and presenteeism.

Adalimumab has been reported to reduce corticosteroid burden in patients with non-infectious uveitis.[11 12 19 21–23] In this study, the proportion of patients in quiescence who were corticosteroid-free improved from 51/99 at V1 (52%) to 67/99 at V4 (68%). Mean highest maintenance corticosteroid dose decreased from 28.8 mg/day (V0) to 20.3 mg/day (V4). The relatively high mean corticosteroid dose was driven by steroid-dependent patients (27/106), reflecting a higher real-world corticosteroid dosage than in controlled clinical trials. Some investigators may have been reluctant to taper corticosteroids in patients based on their medical condition. When three patients

Table 2 Summary of reportable events

Patients, n (%)	Full analysis set (N=149)
SAE	13 (9)
AESI	1 (0.7)
Any product complaints	2 (1)
System organ class	
Infections*	4 (2.7)
Eye disorders†	3 (2)
Pregnancy, puerperium, and perinatal conditions	3 (2)

*One event each of appendicitis, atypical pneumonia, meningitis, orchitis, sepsis, and urinary tract infection.
†One event each of eye inflammation and ocular hypertension and two events of glaucoma.
AESI, adverse event of special interest; SAE, serious adverse event.

requiring higher corticosteroids were excluded, mean prednisone equivalent dose decreased from 18.5 mg/day (V0) to 10.6 mg/day (V4). Another multicentre study evaluating real-world treatment patterns in 580 patients with non-infectious uveitis reported that 62% (360/580) received systemic corticosteroids; mean dose was 38–46 mg/day of prednisone equivalent.[24] Despite progress in uveitis treatment, real-world scenarios show the continued use of long-term high-dose corticosteroids, highlighting the unmet needs in disease management.

Limited real-world studies are available for patients with non-infectious uveitis receiving adalimumab (online supplemental table 2). Although a few studies assessed effects of adalimumab on corticosteroid burden,[19 21 22] only the current prospective study addressed effects of adalimumab on quality of life, HRU, and workability. Unlike the retrospective real-world studies,[19 21 22 25 26] this prospective study included geographically diverse population from 12 countries.

Limitations of this study include an observational non-controlled design and a potential bias associated with self-reported outcomes. VFQ-25 and WPAI-UV are prone to recall, apprehension, and self-presentation bias. HRU assessments were captured by physicians based on patients' reports and may be prone to memory bias. Furthermore, attrition bias may have impact on the effectiveness results (LOCF was used for imputing missing assessments at V4 for patient-reported outcomes). Patients were recruited from large urban academic sites; bias toward a population with more severe or chronic uveitis is possible. Approved NIIPPU therapies other than corticosteroids may have been limited in some regions. Given the observational nature of this study, no steroid tapering schedule was prescribed by the protocol and data on the type and use of corticosteroids to support the exploratory endpoint (eg, impact of adalimumab on corticosteroid use) were collected without the granular details of the dosing schedule. Longer follow-up is needed to further evaluate effects of adalimumab on corticosteroid burden. Although 99/128 (77%) of our patients achieved quiescence at V4 while on low dose (≤7.5 mg/day) corticosteroids, future explanatory and adequately powered studies are needed to further address the corticosteroid-sparing effects of adalimumab. Strengths of this study include the prospective design and a large international cohort of patients with active uveitis (predominantly panuveitis) allowing for a comprehensive overview of patient characteristics, socio-economic aspects, and the effects of adalimumab in a real-world setting.

Patients with active NIIPPU who received adalimumab in routine clinical practice showed improvement in ocular inflammation, quality of life, workability, and HRU; most achieved quiescence during the 12-month follow-up. To date, these results are the first to demonstrate adalimumab effectiveness in improving quality of life while reducing the economic burden of the disease.

Author affiliations
[1]Charité Universitätsmedizin Berlin, Berlin, Germany
[2]Al-Bahar Ophthalmology Center - Al-Sabah Hospital, Kuwait City, Kuwait
[3]Ophthalmology, Royal Victoria Eye an Ear Hospital, Dublin, Ireland
[4]American University of Beirut, Beirut, Lebanon
[5]AbbVie Biopharmaceuticals GmbH, Dubai, UAE
[6]AbbVie Inc, North Chicago, Illinois, USA
[7]Department of Ophthalmology, Semmelweis University, Budapest, Hungary
[8]Department of Ophthalmology, University of Lausanne, Lausanne, Switzerland
[9]Cleveland Clinic Abu Dhabi, Abu Dhabi, UAE
[10]Cleveland Clinic Lerner College of Medicine of CWRU, Cleveland, Ohio, USA
[11]Division of Ophthalmology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[12]Department of Medicine, University of Thessaly, Larissa, Greece

Correction notice The affiliation for Dr Zohar Habot-Wilner has been updated since this article was first published.

Acknowledgements AbbVie funded the study; contributed to its design; and was involved in the collection, analysis, and interpretation of the data and in the writing, reviewing, and approval of the publication. Medical writing support was provided by Natalia Zhukovskaya, PhD, of ICON (Blue Bell, PA), and was funded by AbbVie.

Contributors ON, YG-C, and SA contributed to research design. UP is guarantor.

Funding AbbVie funded the study; contributed to its design; and was involved in the collection, analysis, and interpretation of the data and in the writing, reviewing, and approval of the publication. There was no award or grant number.

Competing interests UP has served as a principal investigator or consultant for AbbVie, Alcon, Allergan, Dompé, Novartis, Santen, Shire, and Thea. CM received research grant funding, speaker fees and honoraria, and conference sponsorship from AbbVie. RH received research grant funding from AbbVie, speaker fees from AbbVie and Amgen, and served as a consultant for Novartis. KJ has served as a principal investigator and consultant for AbbVie. YG-C has served as a principal investigator for AbbVie. SH is an employee of AbbVie and may hold AbbVie stock or options. ON was an employee of AbbVie at the time of the study and is a current contractor of AbbVie and may hold AbbVie stock or options. ZH-W served as a consultant and received speaker fees from AbbVie. SA received research support from AbbVie, Alcon, Allergan, Bayer, Novartis, Roche, Servier, and Xoma.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the ethics committee of the Charité – Universitätsmedizin Berlin, EA2/124/17. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

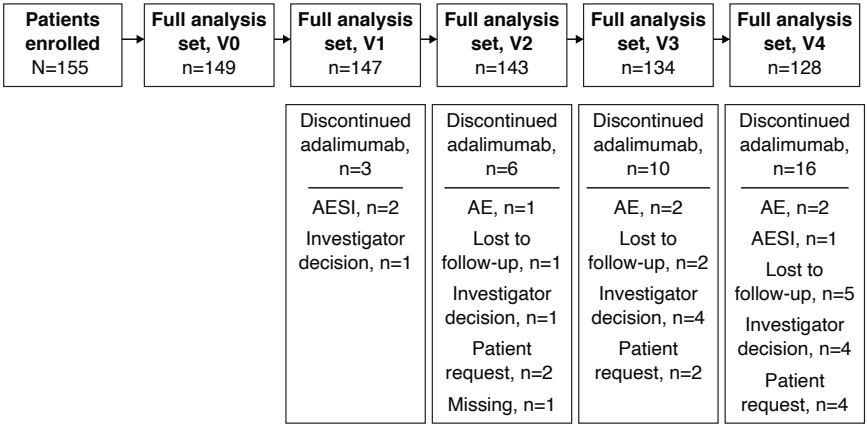
Data availability statement Data are available upon reasonable request.

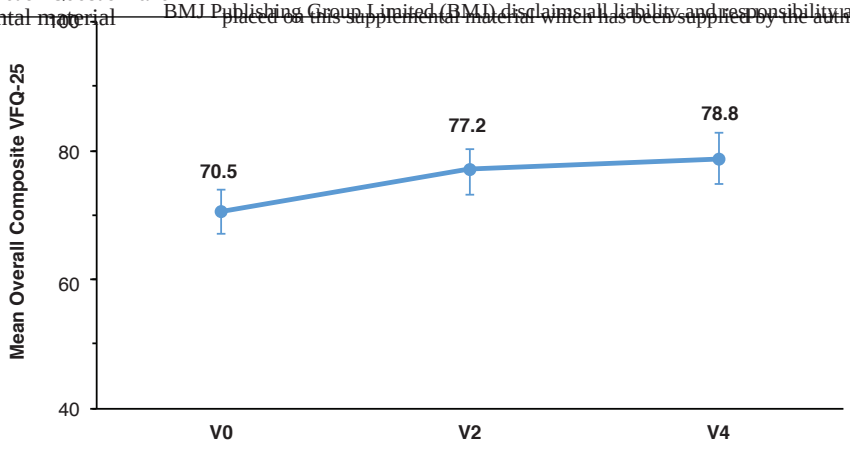
ORCID iDs
Uwe Pleyer http://orcid.org/0000-0002-5569-1473
Conor C Murphy http://orcid.org/0000-0003-2171-0418
Yan Guex-Crosier http://orcid.org/0000-0002-1373-9635
Sofia Androudi http://orcid.org/0000-0002-5303-7793

REFERENCES

1 Rothova A, Suttorp-van Schulten MS, Frits Treffers W, *et al*. Causes and frequency of blindness in patients with intraocular inflammatory disease. *Br J Ophthalmol* 1996;80:332–6.
2 de Smet MD, Taylor SRJ, Bodaghi B, *et al*. Understanding uveitis: the impact of research on visual outcomes. *Prog Retin Eye Res* 2011;30:452–70.
3 Thorne JE, Skup M, Tundia N, *et al*. Direct and indirect resource use, healthcare costs and work force absence in patients with non-infectious intermediate, posterior or panuveitis. *Acta Ophthalmol* 2016;94:e331–9.
4 Sen HN, Vitale S, Gangaputra SS, *et al*. Periocular corticosteroid injections in uveitis: effects and complications. *Ophthalmology* 2014;121:2275–86.
5 Jabs DA, Rosenbaum JT, Foster CS, *et al*. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. *Am J Ophthalmol* 2000;130:492–513.
6 Rosenbaum JT, Bodaghi B, Couto C, *et al*. New observations and emerging ideas in diagnosis and management of non-infectious uveitis: a review. *Semin Arthritis Rheum* 2019;49:438–45.
7 Dick AD, Rosenbaum JT, Al-Dhibi HA, *et al*. Guidance on noncorticosteroid systemic immunomodulatory therapy in noninfectious uveitis: fundamentals of care for uveitis (focus) initiative. *Ophthalmology* 2018;125:757–73.
8 HUMIRA® (adalimumab). *Full prescribing information, AbbVie Inc*. North Chicago, IL, USA, 2016.
9 Jaffe GJ, Dick AD, Brézin AP, *et al*. Adalimumab in patients with active noninfectious uveitis. *N Engl J Med* 2016;375:932–43.

10 Nguyen QD, Merrill PT, Jaffe GJ, *et al*. Adalimumab for prevention of uveitic flare in patients with inactive non-infectious uveitis controlled by corticosteroids (visual II): a multicentre, double-masked, randomised, placebo-controlled phase 3 trial. *Lancet* 2016;388:1183–92.
11 Suhler EB, Adán A, Brézin AP, *et al*. Safety and efficacy of adalimumab in patients with noninfectious uveitis in an ongoing open-label study: visual III. *Ophthalmology* 2018;125:1075–87.
12 Suhler EB, Jaffe GJ, Fortin E, *et al*. Long-Term safety and efficacy of adalimumab in patients with noninfectious intermediate uveitis, posterior uveitis, or panuveitis. *Ophthalmology* 2021;128:899–909.
13 Hassan M, Karkhur S, Bae JH, *et al*. New therapies in development for the management of non-infectious uveitis: a review. *Clin Exp Ophthalmol* 2019;47:396–417.
14 Jabs DA, Nussenblatt RB, Rosenbaum JT, *et al*. Standardization of uveitis Nomenclature for reporting clinical data. Results of the first International workshop. *Am J Ophthalmol* 2005;140:509–16.
15 Nussenblatt RB, Palestine AG, Chan CC, *et al*. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. *Ophthalmology* 1985;92:467–71.
16 Prasad M, Wahlqvist P, Shikiar R, *et al*. A review of self-report instruments measuring health-related work productivity: a patient-reported outcomes perspective. *Pharmacoeconomics* 2004;22:225–44.
17 Mangione CM, Lee PP, Gutierrez PR, *et al*. Development of the 25-item National eye Institute visual function questionnaire. *Arch Ophthalmol* 2001;119:1050–8.
18 Sharma SM, Damato E, Hinchcliffe AE, *et al*. Long-Term efficacy and tolerability of TNFα inhibitors in the treatment of non-infectious ocular inflammation: an 8-year prospective surveillance study. *Br J Ophthalmol* 2021;105:1256–62.
19 Bitossi A, Bettiol A, Silvestri E, *et al*. Adalimumab accounts for long-term control of noninfectious uveitis also in the absence of concomitant DMARD treatment: a multicenter retrospective study. *Mediators Inflamm* 2019;2019:1–8.
20 Landewe R, van der Horst-Bruinsma I, Tari S, *et al*. THU0583 Quiescence in Active and Inactive Non-Infectious, Intermediate, Posterior, or Panuveitis in Patients Treated with Adalimumab: Visual I and Visual II Trials. *Ann Rheum Dis* 2016;75:403.1–403.
21 Tang Lee Say TL, Yang V, Fingret JM, *et al*. Adalimumab in patients with vision-threatening uveitis: real-world clinical experience. *BMJ Open Ophthalmol* 2021;6:e000819.
22 Lee JT, Yates WB, Rogers S, *et al*. Adalimumab for the treatment of refractory active and inactive non-infectious uveitis. *Br J Ophthalmol* 2018;102:1672–8.
23 Pirani V, Pelliccioni P, De Turris S, *et al*. Intraocular inflammation control and changes in retinal and choroidal architecture in refractory non-infectious uveitis patients after adalimumab therapy. *J Clin Med* 2020;9:510.
24 Nguyen QD, Hatef E, Kayen B, *et al*. A cross-sectional study of the current treatment patterns in noninfectious uveitis among specialists in the United States. *Ophthalmology* 2011;118:184–90.
25 Park SE, Jun JW, Lee DH, *et al*. The effect of adalimumab in Korean patients with refractory noninfectious uveitis. *Yonsei Med J* 2021;62:177–81.
26 Llorenç V, Cordero-Coma M, Blanco-Esteban A, *et al*. Drug retention rate and causes of discontinuation of adalimumab in uveitis: real-world data from the Biotherapies in uveitis (BioÚvea) Study Group. *Ophthalmology* 2020;127:814–25.




Mean Overall Composite VFQ-25
100
80
60
40
70.5
77.2
78.8
V0
V2
V4

Supplementary Table 1. Number of patients recruited from specific countries.

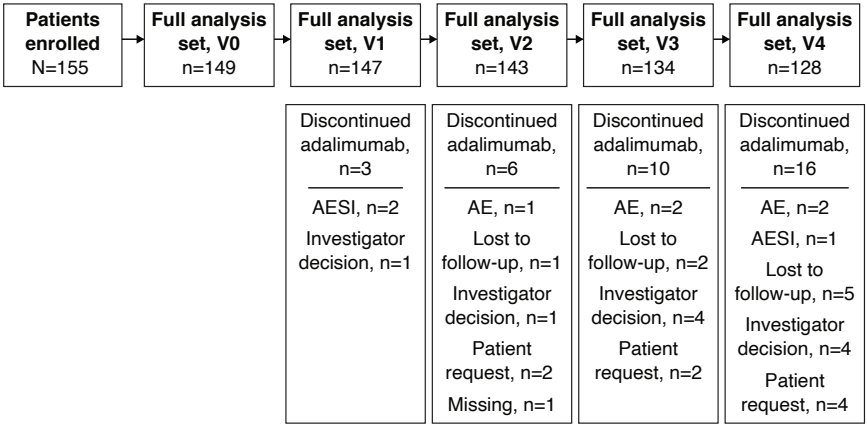
Country	Patients, n
Greece	27
Switzerland	23
Germany	23
Kuwait	17
Hungary	15
Ireland	14
Israel	11
Austria	9
United Arab Emirates	7
Lebanon	6
Colombia	2
Czech Republic	1

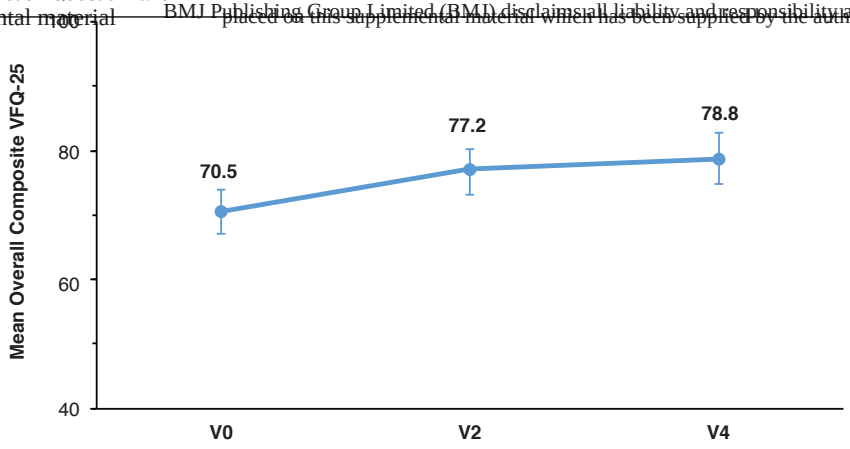
Supplementary Table 2. Real-world studies of adalimumab in patients with noninfectious uveitis.

Study name	Reference	N	Follow up	Primary endpoint results	Secondary endpoint results	Safety	QoL included	HRU included	Steroid dose decreased	Strengths	Limitations
HOPE (International, 12 countries)		149	1 year	91% of pts achieved quiescence at any visit	• 83% of pts maintained response (any visit) • 32% of pts had flares (any visit) • Median VFQ-25 improved from 72.5 (V0) to 88.2 (V4) • Reduced hospital and ER visits at V4 vs V0 • Improved WPAI-UV scores at V4 vs V0 • Steroid daily dose decreased from 18.5 mg (V0) to 10.6 mg (V4)	• Common AEs: infection and eye disorders • Most events were mild to moderate in severity	Yes	Yes	Yes	• Prospective design • Large international cohort • Real-world settings	• Observational design • Selection and attrition bias • Potential differences in access to approved NIIPPU therapies in different regions
Retrospective medical record chart review (single-site, Australia)	Tang Lee Say *BMJ Open Ophthalmol* 2021[20]	46	10 years (4.5 years mean follow-up)	17% of pts had a treatment failure on adalimumab Mean time to treatment failure was 460 days	• Steroid dose reduced to ≤7.5 mg/day (24% pts) or stopped (74%)		No	No	Yes	• Real-world clinical data	• Small sample size • Retrospective design

Retrospective study to assess uveitis control in real-world settings (Korea)	Park *Yonsei Med J* 2021[24]	23 eyes (14 pts)	1 year	AC grade and VH grade improved at 1 year (P<0.05) Central macular thickness was significantly reduced at 1 year (P<0.05)		• No serious AEs	No	No	No	• First study to evaluate efficacy of adalimumab in Korean pts	• Retrospective design • Small sample size
Registry-based observational study (multiple sites, Spain)	Llorenc *Ophthalmol* 2020[25]	392	5 years	39% pts discontinued adalimumab Drug retention rate was 54% at 5 y Median drug retention time was 69 months.		• 8.7% of pts experienced AEs leading to discontinuation (most common were infections, 2.6%)	No	No	No	• Large patient sample • Long-term study	• Retrospective design • Differences in discontinuation criteria between investigators
Retrospective medical chart review (3 referral centers, Italy)	Bitossi *Mediators Inflamm* 2019[19]	106	1 year	Ocular control achieved in 83% of patients at 1 year	• Visual acuity was stable or improved Median daily steroid dose was 10 mg at baseline and 2.5 mg at 1 year.	• 7 pts had mild to moderate AEs	No	No	Yes	• Large cohort, long-term follow-up	• Retrospective design
Retrospective chart review (multicenter)	Lee *Br J Ophthalmol* 2018[21]	37 eyes (22 pts)	18 months	Daily steroids reduced to ≤10 mg in 75% pts at 6 wks	• 90% of eyes had 2-step improvement in AC grade at 6 months • Improvement in VH grade in 60% of eyes	• No serious AEs	No	No	Yes		• Retrospective design

AC=anterior chamber; AE=adverse events; HRU=health resource utilization; QoL=quality of life, TEAE=treatment emergent adverse events; pts=patients; VFQ= visual function questionnaire; VH=vitreous haze, wk=week.




Mean Overall Composite VFQ-25
100
80
60
40
70.5
77.2
78.8
V0
V2
V4

Supplementary Table 1. Number of patients recruited from specific countries.

Country	Patients, n
Greece	27
Switzerland	23
Germany	23
Kuwait	17
Hungary	15
Ireland	14
Israel	11
Austria	9
United Arab Emirates	7
Lebanon	6
Colombia	2
Czech Republic	1

Supplementary Table 2. Real-world studies of adalimumab in patients with noninfectious uveitis.

Study name	Reference	N	Follow up	Primary endpoint results	Secondary endpoint results	Safety	QoL included	HRU included	Steroid dose decreased	Strengths	Limitations
HOPE (International, 12 countries)		149	1 year	91% of pts achieved quiescence at any visit	• 83% of pts maintained response (any visit) • 32% of pts had flares (any visit) • Median VFQ-25 improved from 72.5 (V0) to 88.2 (V4) • Reduced hospital and ER visits at V4 vs V0 • Improved WPAI-UV scores at V4 vs V0 • Steroid daily dose decreased from 18.5 mg (V0) to 10.6 mg (V4)	• Common AEs: infection and eye disorders • Most events were mild to moderate in severity	Yes	Yes	Yes	• Prospective design • Large international cohort • Real-world settings	• Observational design • Selection and attrition bias • Potential differences in access to approved NIIPPU therapies in different regions
Retrospective medical record chart review (single-site, Australia)	Tang Lee Say *BMJ Open Ophthalmol* 2021[20]	46	10 years (4.5 years mean follow-up)	17% of pts had a treatment failure on adalimumab Mean time to treatment failure was 460 days	• Steroid dose reduced to ≤7.5 mg/day (24% pts) or stopped (74%)		No	No	Yes	• Real-world clinical data	• Small sample size • Retrospective design

Retrospective study to assess uveitis control in real-world settings (Korea)	Park *Yonsei Med J* 2021[24]	23 eyes (14 pts)	1 year	AC grade and VH grade improved at 1 year (P<0.05) Central macular thickness was significantly reduced at 1 year (P<0.05)		• No serious AEs	No	No	No	• First study to evaluate efficacy of adalimumab in Korean pts	• Retrospective design • Small sample size
Registry-based observational study (multiple sites, Spain)	Llorenc *Ophthalmol* 2020[25]	392	5 years	39% pts discontinued adalimumab Drug retention rate was 54% at 5 y Median drug retention time was 69 months.		• 8.7% of pts experienced AEs leading to discontinuation (most common were infections, 2.6%)	No	No	No	• Large patient sample • Long-term study	• Retrospective design • Differences in discontinuation criteria between investigators
Retrospective medical chart review (3 referral centers, Italy)	Bitossi *Mediators Inflamm* 2019[19]	106	1 year	Ocular control achieved in 83% of patients at 1 year	• Visual acuity was stable or improved Median daily steroid dose was 10 mg at baseline and 2.5 mg at 1 year.	• 7 pts had mild to moderate AEs	No	No	Yes	• Large cohort, long-term follow-up	• Retrospective design
Retrospective chart review (multicenter)	Lee *Br J Ophthalmol* 2018[21]	37 eyes (22 pts)	18 months	Daily steroids reduced to ≤10 mg in 75% pts at 6 wks	• 90% of eyes had 2-step improvement in AC grade at 6 months • Improvement in VH grade in 60% of eyes	• No serious AEs	No	No	Yes		• Retrospective design

AC=anterior chamber; AE=adverse events; HRU=health resource utilization; QoL=quality of life, TEAE=treatment emergent adverse events; pts=patients; VFQ= visual function questionnaire; VH=vitreous haze, wk=week.